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Conference Report

B2B: Prostate Cancer Summary

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The 6th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 44th Annual Congress of the Société Internationale d'Urologie, was held on 25 October 2024, in New Delhi, India, and transmitted live on the *SIU@U* Congress platform. The third session, on prostate cancer (PCa), took place in the afternoon and was moderated by Dr. Gagan Prakash (India). This session comprised presentations on alternatives to prostate-specific antigen (PSA) screening for PCa and optimizing post-prostatectomy continence. It continued with a debate on the need for lymph node dissection (LND) in conjunction with prostate-specific membrane antigen (PSMA) positron emission tomography (PET), as well as a panel discussion on management of biochemical recurrence (BCR). The session concluded with a presentation on advances in theranostics for PCa.

The first presentation was given by Dr. Caroline Moore (United Kingdom), who spoke about alternatives to PSA screening for PCa. The traditional tools used for PCa screening, she reminded the audience, are digital rectal examination (DRE), PSA testing, transrectal ultrasound (TRUS), and random 12-core prostate biopsy. Limitations of a single PSA screening test were demonstrated in the CAP study, in which a single PSA test vs. no test yielded no differences in rates of mortality or PCa detection over 15 years [1]. Repeated testing was evaluated in the ERSPC trial, where a PSA $\geq$ 3 ng/mL or an abnormal DRE triggered standard biopsy, and men who screened negative were re-checked. Over 16 years, this approach led to 20% reduction in mortality, but more than 50% of the cancers diagnosed were low risk (LR), and about 75% of biopsies were ultimately deemed unnecessary (results were no cancer or very LR cancer) [2]. Dr. Moore argued that this kind of screening likely does more harm than good at the population level.

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Modern screening, she said, should reduce PCa deaths by finding the most harmful cancers using the best tests available. It should also minimize harm, notably overdiagnosis, which leads to anxiety and unnecessary re-testing as well as overtreatment. Modern tools that may offer this balance include magnetic resonance imaging (MRI) and genetic screening.

The first study to evaluate the potential of MRI screening was PROSTAGRAM, in which 411 men aged 50 to 69 years were invited via their primary care practices and community recruitment for a prostate health check. These men received a multiparametric MRI (mpMRI), TRUS, and PSA test. If the tests were positive (MRI Prostate Imaging-Reporting and Data System [PI-RADS] score $\geq$3 plus TRUS thresholds $\geq$3 or $\geq$4 or PSA $\geq$3 ng/mL), they received a 12-core biopsy. This was a blinded, paired, screen-positive design study. Importantly, participants represented a range of ethnicities, including 38% white, 32% black, and 23% Asian men [3].

Using PSA $\geq$ 3 ng/mL as a cut-off led to a biopsy rate of 10%. With PI-RADS MRI score $\geq$ 3 as cut-off, the biopsy rate was 18%. A more reasonable biopsy rate of 10.5% was achieved using a PI-RADS MRI score $\geq$ 4. Using this cut-off, the MRI would have a sensitivity of 65% and specificity of 82% [3].

In the ReIMAGINE study, 2096 men aged 50 to 75 were invited for screening, consisting of MRI and PSA, from 6 primary care practices. A positive screen was defined as a PSA density $\geq$ 0.12 ng/mL^2 or a lesion visible on MRI. Those who screened positive went on to receive an mpMRI, and if the mpMRI was positive, they underwent a biopsy. Clinically significant disease was defined as Gleason score $\geq$3 + 4 based on biopsy of transperineal targeted and systematic cores [4].

Once again, effort was made to capture a multiethnic population but with less success, as white men were far more likely than black men to respond to a written invitation from their general practitioner. Participants were 85% white, 5% Asian, and 4% black. Overall, 16% of participants had a positive MRI, and just over half of these (8% of men who took part) were found to have clinically significant PCa. Among men with a negative MRI but a positive PSA density screening test, 25% had clinically significant PCa. The rate of negative biopsy was very low. Notably, more than half of men with a clinically significant PCa that was found on screening MRI had a PSA < 3 ng/mL, and a substantial portion of these PCa were clinically significant cancers. In fact, of all 25 MRI-detected cancers, 23 were clinically significant. PSA density $\geq$0.12 ng/mL^2 alone identified only 5 PCa. Of these, 4 were clinically significant [4].

The next step for Dr. Moore and her team is the ongoing TRANSFORM study, a robust UK-based trial of modern screening approaches in PCa that will assess acceptability, clinically effectiveness, and cost-effectiveness of different strategies. The team also aims to assess barriers to access and ways to facilitate equitable engagement across the population. In addition, they plan to create a data, imaging, histological, and biological repository of information related to PCa [5].

The study has 3 stages. In the first stage, eligible men in primary care with no history of PCa will be randomized to a control arm or to receive an invitation to pilot new screening interventions. Those who accept the invitation will be randomized to 1 of 4 prostate health screens: PSA $\geq$ 3 ng/mL leading to MRI, PSA $\geq$ 1 ng/mL leading to MRI, MRI regardless of PSA level, or polygenic risk score $\geq$ 3.5% leading to MRI. During this 3-year phase of the study, where 12,500 men will undergo a prostate health check, the investigators will determine how best to carry out the large screening trial planned for phase 2, in which 150,000 to 300,000 men will be recruited to receive 1 or 2 screening interventions. During this 6-year phase of the study, they will build a biobank with clinical and imaging data alongside a fluidic and histological archive. In the final stage, the investigators will assess

long-term primary outcomes from the trial through linkage to national databases over an additional 10 years [5].

During a Q&A, Dr. Prakash said that a major transformation in PCa screening will take a decade. He asked what changes are likely to occur in the meantime. Dr. Moore replied that, in the United Kingdom, an informed man who asks his physician for a PSA test can now receive one. If PSA is high, patients will automatically receive an MRI. This approach causes health inequality based on which men know to ask for a PSA test. Thus, several outreach schemes are in place to encourage a wider range of men to ask for a PSA test, particularly in underrepresented communities. Not all of these have been successful, however.

The next presentation was given by Dr. Franck Bladou (France), who discussed strategies for optimizing post-prostatectomy continence. He said that many PCa patients are reluctant to undergo surgery, largely due to concerns about post- prostatectomy urinary incontinence (PPUI). In the medical literature, reported rates of PPUI vary dramatically, from 6% to 69% [6,7]. This is because PPUI risk varies depending on patient population and the definition of incontinence [6,7]. The best definition of continence, Dr. Bladou suggested, is measured via patient reports and defined by the complete lack of need for urinary pads. Using this definition, the rate of PPUI approaches 60% to 70% [6,7].

There are several factors involved in maintaining continence. A 2012 systematic review and meta- analysis reported the rate of PPUI at 1 year following radical prostatectomy (RP) to be between 4% and 31%. Preoperative factors that predicted PPUI were age, body mass index, comorbidity index, lower urinary tract symptoms (LUTS), and prostate volume. Few comparative studies have evaluated surgical technique and rates of PPUI but, in this meta-analysis, robotic RP had better PPUI outcomes than open RP (odds ratio [OR] = 1.53, $p = 0.03$) or laparoscopic RP (OR = 2.39, $p = 0.006$) [8]. Nevertheless, other studies have had opposing findings.

Factors that affect risk of PPUI include patient characteristics (e.g., comorbidities and anatomy) and surgeon factors (e.g., experience), as well as disease features/stage/grade, intraoperative technique, and postsurgical recovery and care [9]. Performing RP while minimizing anatomical damage has been studied extensively. Based on anatomical studies, the posterior part of the bladder neck is an important anatomical structure with respect to maintaining continence [10]. Recent technical innovations that have been used to reduce rates of PPUI include preserving key structures such as the bladder neck and endopelvic fascias. Another innovation is to reconstruct the posterior rhabdosphincter, retropubic anterior suspension, and vesicourethral anastomosis. Finally, the bladder neck plication and bladder neck suspension can be reinforced [9].

Rocco et al. developed a simple technique to reconstruct the posterior portion of the rhabdosphincter via the "Rocco stitch". What was particularly impressive in his series was the speed of recovery [11]. A more complex reconstruction technique was published by Porpiglia et al. This approach involves using 3 different sutures on the posterior wall, urethrovesical anastomosis, and anterior reconstruction [12]. Initial results were impressive, said Dr. Bladou, with a 24-week continence rate of 98% [12]. Dr. Bladou uses this technique himself, except that he does only 2 posterior reconstructions. In a systematic review and meta-analysis, long-term results of this approach were reported to be good, particularly with respect to recovery at 6 months, which appears to be further advanced with reconstruction [8].

Dr. Bladou's own team compared their outcomes of robot-assisted RP using the Rocco stitch vs. total anatomical reconstruction and showed slightly higher continence rates after 1 year with the Rocco stitch (81% vs. 73%). He warned, however, that the patient

populations were quite different. The total reconstruction patients were more likely to have T3 disease, with more LNDs and less nerve sparing.

Pelvic floor muscle training, both before and after RP, has been shown to help promote continence recovery. Milios et al. published a study in which 50 patients performed pelvic floor muscle training consisting of 6 series of 10 fast contractions (1 s) and 10 maintained contractions (10 s) every day in an upright position starting 5 weeks before and continuing until 12 weeks after RP. A control group of 47 patients conducted 3 series of 10 contractions of 10 s per day, in a lying, sitting, and upright position. The experimental group had double the continence recovery rate of the control group by 12 weeks [13]. The challenge is that there are no standard pelvic floor muscle training exercises specifically for recovering continence following RP [14].

PPUI is not caused just by an impaired occlusion mechanism. Urodynamic studies will reveal reduced bladder capacity in about one-third of RP patients [15]. This is a problem that can be managed with medication used for treatment of detrusor muscle hyperactivity. The antidepressant duloxetine also showed benefits in one small study [16].

To optimize post-prostatectomy continence, Dr. Bladou concluded, rehabilitation, enhanced recovery after surgery, and pre- and postoperative physiotherapy are crucial. As surgeons, it is important to optimize technical skills. Patients should be made aware of risk factors for PPUI and the postoperative management that will be needed. They should be closely followed up during the postsurgical continence recovery period. Dr. Bladou feels posterior reconstruction in particular is a good surgical approach because it hastens recovery of continence.

During a Q&A session, an attendee asked whether there are any red flags that can be identified prior to surgery in patients with PCa that suggest a high likelihood of PPUI, in which case radiation may be a better treatment option than RP. Dr. Bladou replied that he has these discussions with every patient prior to selecting a treatment, and this includes the input of a radiation oncologist. Usually, patients who are not good candidates for surgery are also not good candidates for radiotherapy (RT) either. Another attendee asked if Dr. Bladou has reviewed his PPUI rate over the years and whether he has identified any factors that have contributed to improvements in continence rates. Dr. Bladou replied that there is clearly a surgical learning curve, and he addresses that by having trainees follow a step-by-step procedure. He also has found that robot-assisted surgery has improved outcomes.

Next was a debate on whether LND is necessary in the era of PSMA PET. Dr. Prakash began by arguing that it is *not* necessary. He opened the debate by explaining that clinicians generally assume that cancer progression always follows a similar, Halstedian pattern, but that is not true for all cancers, including PCa.

A potential benefit of extended pelvic LND (ePLND) is to help identify patients who may benefit from adjuvant treatment. However, this can also be accomplished by examining PSA levels. While an ePLND could theoretically cure some patients, no high-quality evidence is available to support this claim. In addition, ePLND adds to surgical time during RP, which can contribute to complication risk.

Dr. Prakash evaluated the available evidence on whether ePLND improves oncological outcomes. A systematic review and meta-analysis of 66 studies and 275,269 patients revealed that ePLND is likely a good staging procedure, but it has no proven therapeutic effect and is associated with worse intraoperative and perioperative outcomes [17]. In a randomized controlled trial (RCT) comparing 700 patients who received limited pelvic LND (PLND) with 740 who received ePLND, the rate of positive nodes was 12% and 14%, respectively. With a median follow-up of 3.1 years, there was no significant difference in the rate of BCR between the groups (hazard ratio = 1.04, 95% confidence interval [CI] 0.93–1.15; $p = 0.5$) [18].

There is evidence that conducting an ePLND can cause a significant increase in the rate of complications, more than doubling it, from 8.2% to 19.8%, when comparing limited PLND with ePLND ($p < 0.001$) [19]. In addition, a systematic review of the literature revealed that a blind PLND during robot-assisted RP could be associated with substantial adverse effects, which include lymphocele, deep vein thrombosis, and pulmonary embolism [20]. More recently, Gupta et al. have challenged the concept of removing the lymph nodes. Not only is blind PLND not beneficial, it may also be detrimental because pelvic lymph nodes help protect against cancer and could play an increasingly important role as more advanced immunotherapy becomes available [21].

In one of the largest series published to date, the negative predictive value of PSA in terms of identifying positive lymph nodes was 87% overall and 81% among patients with high-risk (HR) disease [22]. This can be improved by adding PSMA PET to existing nomograms. In one study, use of a 5% cut-off would have spared 47% of the ePLND procedures (vs. 13% for the Briganti 2019 nomogram) at a cost of missing only 2.1% of positive lymph node cases [23]. Dr. Prakash and his team conducted a retrospective review of 205 patients who underwent robot-assisted RP between 2015 and 2022 and who received a PSMA PET prior to RP. The 15 patients who were identified as node positive on PSMA PET were excluded, leaving 190 patients in the analysis. Among these patients, 20 had negative PSMA PET scans but were found to have positive nodes on lymphadenectomy. Of these 20 false negatives, 3 were intermediate risk (IR). The maximum standardized uptake value (SUVmax) at the primary site of the prostate in these patients was much higher in all those cases (i.e., 26.6, 40, and 54) than the median SUVmax of the remaining 46 IR cases that were true negatives (median 26.4 vs. 12.8, $p < 0.002$). Similarly, among the 17 HR cases with false negatives, median SUVmax was 24.3, which was much higher than the median SUVmax (median 13.5 among the 118 HR cN0 cases who were true negatives, $p < 0.001$) [24]. Dr. Prakash explained that this likely means that the SUVmax at the primary site of the prostate can help identify patients with aggressive pathology who might have metastatic disease that is not detected with PSMA PET and could likely benefit from ePLND.

LND for other solid tumours is often radioguided, and there is potential for increased use of PSMA radioguided surgery in PCa. A DROP-IN ß-probe for robotic radioguided surgery for PCa has already been validated [25], and additional work has recently been published on its standardization [26]. An RCT has been initiated in which all patients undergo PSMA PET/ computed tomography (CT) and are then randomized to either robot-assisted RP with ePLND or robot-assisted RP with the addition of ePLND only in patients for whom PSMA findings indicate the need [27].

Dr. Prakash concluded by saying that identifying tumour biology via SUVmax of the primary tumour, selecting patients via PSMA-based nomograms, and improving technical manoeuvre via radioguided surgery may make ePLND unnecessary in the vast majority of patients.

Next, Dr. Silvia Secco (Italy) was asked to argue in favour of the necessity of LND in the era of PSMA PET. An ideal diagnostic test, she began, has a high sensitivity, specificity, and accuracy. The question remains how accurate PSMA PET is for lymph node staging. Research indicates that PSMA PET is more sensitive than other diagnostic tests, including MRI, CT, and bone scanning [28–30], and this is reflected in the guidelines [31]. Nevertheless, a 2024 update of the European Association of Urology (EAU) guidelines points out that while PSMA PET/CT has a good sensitivity for identifying positive lymph nodes, it is unclear whether patients with metastases detectable only with PSMA PET/CT or whole-body MRI should be managed using systemic therapies only, or whether they should receive aggressive local and metastases-directed therapies [32].

Current research suggests that PSMA PET offers a sensitivity of about 40% and specificity of about 95% to 98% for pelvic node involvement [33,34]. This does not represent a high enough accuracy, said Dr. Secco, because it may still overlook small lymph node metastases (i.e., <5 mm) [30,35] and cannot replace ePLND [36].

Today, LND provides optimal staging when compared with any imaging with possible oncological benefit and helps guide patient selection for early salvage therapies, according to the latest EAU guidelines update [32]. The potential for false negatives with PSMA PET is a real concern for clinicians. Dr. Secco reported that one of her patients decided not to undergo ePLND, experienced a BCR, and with restaging was found to have positive lymph nodes. Guidelines continue to recommend ePLND [31], despite the procedure having known benefits and harms [37].

Ultimately, additional research is needed to confirm whether ePLND continues to be essential. To provide the best care to patients, clinical information should be combined with PSMA PET findings and nomograms. Together, this might provide enough information for most patients, thus eliminating the need for ePLND. An international, multicentre study examined the benefits of incorporating PSMA PET into existing nomograms in order to predict pelvic lymph node metastatic disease in patients with PCa. The performance of 3 nomograms was assessed in 757 patients undergoing RP and ePLND. The addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models, yielding cross-validated areas under the curve of 0.76 (95% CI = 0.70–0.82), 0.77 (95% CI = 0.72–0.83), and 0.82 (95% CI = 0.76–0.87) for each nomogram [38].

Finally, the decision to proceed with ePLND must be shared with the patient. It is fundamental that patients be fully informed on benefits and risks of ePLND, including both functional and oncological outcomes.

In the future, Dr. Secco concluded, there may be the opportunity to perform sentinel node surgery guided by a technetium-99 m probe [39]. Several investigations into this modality are ongoing, but the technology remains expensive. Other probes that can be used during robot-assisted RP to help identify metastases missed by PSMA PET include the DROP-IN ß-probe [25]. In addition, advances in artificial intelligence and machine learning will provide better ways to consolidate all the information available to help identify lymph node metastases [40].

Next was a panel discussion on management of BCR, which was moderated by Dr. Sanjai Addla (India). Panellists were Priyamvada Maitre (India), Senthil Rajappa (India), and Henry Woo (Australia). Dr. Addla started the discussion by pointing out that different specialists have differing definitions of BCR. He asked the panellists to define BCR under various clinical circumstances. Post RP, Dr. Woo defines BCR as a threshold PSA of 0.2 ng/mL, while Dr. Maitre uses the PHOENIX definition, which is a PSA of +2 ng/mL above nadir and rising on 2 separate occasions. Post RP and RT, Dr. Woo defines BCR as threshold PSA of 0.2 ng/mL, and Dr. Maitre uses 0.2 ng/mL above nadir, but she would expect the nadir to be 0, so her criteria are similar to Dr. Woo's. Post focal therapy, panellists agree there is no clear definition of BCR.

A primary objective of treating BCR, panellists agree, is to improve overall survival (OS). Dr. Maitre added that once OS, cancer-specific survival, and metastasis-free survival (MFS) are addressed, then the next step would be to target androgen deprivation therapy (ADT)-free survival. Dr. Rajappa noted that achieving good quality of life is also important, and ADT-free survival is a surrogate of that objective.

The panellists agreed that intermediate clinical endpoints are important, and Dr. Addla presented evidence that MFS is a strong surrogate for OS in the setting of localized PCa [41]. In an aggregate meta- analysis that evaluated surrogate markers for OS in localized PCa, said Dr. Addla, MFS was the most robust, but he was surprised to see how

poorly the other surrogate markers fared, particularly rates of local failure and time to distant metastases [42]. Dr. Rajappa pointed out that in the setting of BCR, while MFS remains a surrogate for OS, it is not as robust.

Panellists agreed that not all BCR needs to be treated. According to research published in 1999, the natural history and progression of PCa following PSA elevation after RP is such that, without any treatment, the median time from BCR to metastasis is 8 years, and median time from metastasis to death is 5 years [43]. This may not be representative of current RP cohorts, however. Dr. Woo noted that there has been a major evolution in this group of patients in the past 25 years, including an evolution in Gleason scoring and imaging. Nevertheless, this study remains a good basis on which to justify treatment of BCR.

Risk stratification is important for determining which BCR patients should be treated. A 2019 study revealed that HR PCa patients following the EAU criteria have a higher probability of metastasis and mortality after RP. Following the EAU criteria, Dr. Addla asked how panellists manage LR patients whose PSA is rising post RP. Dr. Rajappa and Dr. Maitre would opt for patient reassurance, since additional testing might yield findings that may or may not result in better outcomes with active treatment. Dr. Woo would not rule out RT because there is a close relationship between success of RP and RT and PSA level. Over the years, the degree to which clinicians are willing to not recommend active treatment with rising PSA is diminishing, with some radiation oncologists recommending not to wait until a threshold of even 0.1 ng/mL before offering RT [44].

Next, Dr. Addla discussed the role of imaging in BCR. Panellists agreed that the majority of their patients with a rising PSA would receive PSMA PET, sometimes even when it is not strictly indicated. Dr. Addla pointed out that 33% of patients with a PSA < 0.2 ng/mL would have a positive PSMA PET [45]. Dr. Woo replied that a PSMA PET can change clinical management if it shows metastatic disease, but a negative PSMA PET should not be a deterrent for offering RT. In fact, a recent study demonstrated that men with BCR and a negative PSMA PET fare better with RT than without [46].

Regarding isotopes used in PSMA PET, the panellists agreed that it is down to personal preference. Dr. Woo likes fluorine-18 DCFPyL/fluciclovine because it has a relatively long half-life, unlike gallium-68. It is underestimated, he said, how much effect uptake time has on SUVmax. In the EMPIRE-1 trial, post-RP PCa patients with no systemic metastases on conventional imaging were randomized to a conventional PET scan or to conventional imaging plus fluorine-18 fluciclovine PET/CT [47]. The overall positive rate for pelvic lymph nodes on fluorine-18 fluciclovine PET/CT among patients with a PSA < 1 ng/mL was 63.6%. Among patients with a PSA > 1 ng/mL, 18.2% had positive lymph nodes at extrapelvic sites on fluorine-18 fluciclovine PET/CT [48]. Event-free survival was impacted by changes in treatment plan that were based on fluorine-18 fluciclovine PET/CT findings [48].

Dr. Addla asked how panellists would treat patients with positive lymph nodes at extrapelvic sites on fluorine-18 fluciclovine PET/CT. Dr. Maitre would not give local RT but instead would initiate ADT. Dr. Rajappa noted that oligometastatic RT in this setting could be employed as a way to expand the ADT-free interval, although the patient in this setting could also be treated with oligometastatic RT plus ADT or ADT alone. Such a decision would need to be made on an individual patient level, as there is no evidence indicating one approach is better than the other. Dr. Woo would offer pelvic RT as well as RT to the prostate bed. Performing PLND brings one close to the prostate bed and could remove the possibility of irradiating that area if it is spared.

The EMPIRE-1 study demonstrated that PSMA-PET in BCR patients resulted in higher positivity rates than conventional imaging, had an impact on management in 35% of patients, and resulted in better outcomes [48]. Based on this, Dr. Addla asked panel-

lists whether PSMA-PET should become the standard investigative tool in this setting. Dr. Rajappa said this is too broad a conclusion to draw from a single small phase 2 study. Although he would likely use PSMA-PET in clinical practice in this setting, there is no robust evidence indicating it would ultimately improve OS.

Early salvage RT is the standard of care, said Dr. Addla, but what remains controversial is whether ADT should be added as well. In the RADICALS-HD trial, short-course (6-month) ADT was compared with long-course (24-month) ADT in combination with RT for salvage in PCa patients. The 10-year MFS was superior with the long-course treatment (hazard ratio = 0.773, 95% CI = 0.612–0.975), but no significant difference in OS has yet been detected [49].

Dr. Addla asked panellists which of their salvage RT patients they consider for ADT. Dr. Maitre recommends salvage RT to patients who are IR and HR based on the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score, with HR patients receiving a longer duration of therapy than IR patients. Dr. Rajappa emphasized that it remains unknown which patients benefit from ADT in this setting, but the evidence suggests that the patients most likely to benefit are HR and that longer duration of therapy is better than shorter. He would not use ADT in patients with 0.2 ng/mL PSA but would consider it for someone with 0.5 ng/mL PSA and HR features. Which ADT agents to use also remains an open question. It is important that the risk of dying from ADT is not higher than the risk of dying from cancer. Dr. Woo would also give ADT to HR patients, but added that there is some conjecture over which IR patients should receive it. The decision should be made in conjunction with the patient.

In the EMBARK trial, patients with a PSA indicative of significant risk for time to PCa-specific mortality were randomized to enzalutamide, leuprolide, or both agents together. Among patients who achieved a PSA < 0.2 ng/mL at 37 weeks, treatment was suspended [50]. Dr. Rajappa agreed that the deintensification was a good thing to include in this trial, but he would have liked to see a fourth arm in which treatment was initiated only upon identification of metastasis. Dr. Maitre agreed that an enzalutamide monotherapy arm was acceptable to have in a trial setting.

Overall, 25% of patients recruited into the EMBARK trial had not received prior RT in a salvage setting. Dr. Addla asked panellists whether, if the trial was running in their centre, they would have recommended eligible patients to enrol in the trial or consider RT first. Dr. Woo agreed that eligible patients should be enrolled in clinical trials. Dr. Rajappa added that the trial investigators should have reported why those patients did not receive RT. Dr. Woo explained that this likely happened because many of those were very HR patients with rapidly rising PSA levels, to the point where RT would no longer be a treatment option.

The primary endpoint of EMBARK was MFS. To date, median OS was not reached, but the stratified hazard ratio for death was better with combination therapy than with leuprolide alone (hazard ratio = 0.59, 95% CI = 0.38–0.91), as was MFS (hazard ratio = 0.42, 95% CI = 0.30–0.61). In addition, enzalutamide monotherapy was superior to leuprolide monotherapy with respect to MFS (hazard ratio = 0.63, 95% CI = 0.46–0.87) [50]. Longer follow-up is required to evaluate the OS, but Dr. Rajappa pointed out that some of the patients in the trial may receive other therapies in the meantime that might confound the final findings. Dr. Maitre said she would have liked to see PSMA data on these patients, but without the availability of imaging she would use the EMBARK trial data to inform treatment in post RP and RT patients with BCR.

At the end of 9 months, 91% of patients in the combination therapy arm of EMBARK had a PSA < 0.02 ng/mL, making them eligible for de-intensification, compared with 70% on leuprolide and 86% on enzalutamide monotherapy. Therapy was stopped for

up to 20 months on combination therapy vs. 17 months with leuprolide and 11 months with enzalutamide. Dr. Rajappa agreed that these are clinically relevant data because a 20-month break could produce a significant improvement in patient quality of life. When determining whether to use combination therapy in patients, however, he highlighted the need for patients to understand the risk of death from both cancer- and noncancer-specific causes. If patients agree to active therapy, he would probably recommend the combination of enzalutamide plus leuprolide because it helps patients to achieve PSA nadir sooner and keeps patients off ADT longer, which will likely benefit quality of life. Dr. Woo largely agreed, but highlighted that there may be a role for enzalutamide monotherapy, as it can result in supernormal levels of testosterone, which can allow patients to retain their libido and sexual activity.

The take-home messages of the discussion, concluded Dr. Addla, are that risk stratification is important to guide therapy, MFS is a surrogate for OS, and 2 years of ADT with salvage RT is appropriate for HR patients. He also explained that intensification with ADT plus enzalutamide should be considered and deintensification in good responders is a possibility.

The last presentation was given by Dr. Damien Bolton (Australia) on advances in theranostics in HR PCa. PSMA staging of PCa is typically conducted with gallium-68 of fluorine-18 isotopes to detect the presence of metastatic disease. PSMA theranostics refers to use of a ß-emitting agent ligated to the same PSMA tracers used for diagnosis, but this time in treatment. For instance, lutetium-177 binds to the antigen on the surface of cells to produce a therapeutic response.

While other agents are available, lutetium-177 is ideally suited to this setting because of its short path length (about 1 mm) and small penetration (about 0.3 mm). Its 6.7-day half-life means it will be available throughout the entire telophase cycle of division of metastatic cells. It offers a crossfire effect due to the short ß-emitter length, which means it targets the entire surface of the cells. Histological studies indicate it will treat all tumours that are at least 1 mm in dimension and is as safe as gallium-68 use in the diagnostic setting.

Clinical and radiologic responses with lutetium-177 PSMA-617 radionucleotide (LuPSMA) in metastatic castration-resistant PCa was first demonstrated in a phase 2 single-centre, single-arm study [51]. Nevertheless, a major clinical unmet need is better treatment for localized HR PCa, for which neoadjuvant strategies have failed to improve BCR in patients who have undergone RP and RT. In this setting, LuPSMA offers some hope [52–54].

Bolton and colleagues published the LuTectomy study of 20 men with biopsy-proven PCa and at least 1 HR feature. In all patients, PSMA PET revealed no distant metastases, but SUVmax in the primary lesion in the prostate had to be $\geq$20. Half the men received 1 cycle of LuPSMA, and the other half received 2 cycles, spaced 6 weeks apart. Six weeks after their final cycle, all men underwent a second staging PSMA PET followed by robot-assisted RP with LND. The 3-year planned follow-up remains ongoing [55].

At the outset of the study, median patient age was 66 years and median PSA was 18 ng/mL. Most had higher-stage tumours, and 19 of 20 were MRI PI-RADS stage 4 or 5. Median SUVmax was 31 [55].

The primary endpoint was dosimetry of radiation received by the tumour, based on PSMA PET. Median absorbed radiation dose was 19.6 Gy in the prostate, 37.9 Gy in the nodes, and 35.5 Gy in all lesions. Secondary endpoints included overall safety and surgical safety. Radiation dose to nearby organs and healthy tissue was within safety limits (median 2.4 Gy for the parotid glands, 2.7 Gy for the kidneys, and 0.13 Gy for the bone marrow). There were minimal high-grade adverse effects (one grade 2 and no grade 3–5 events). The most common adverse event was fatigue. Estimated blood loss during surgery was within

typical range (185 mL). Surgeons reported that surgery was as expected in 75% of cases and slightly more difficult in 25%. No patient required transfusion, and all 10 complications up to 90 days were graded as Clavien 1 or 2 [55].

Median PSA reduction was 49%, and 45% of patients had a reduction in PSA of 50% or more. After 13.8 months of follow-up, BCR-free survival was 80%. Histological findings demonstrated evidence of response within the prostate. This included areas of stromal fibrosis, reduced tumour cell density, cytoplasmic vacuolation, and gland atrophy, as well as extracellular mucin deposition. Overall, 80% of patients had a partial response, 5% had minimal residual disease, and 15% had no response [55].

Currently available data indicate that LuPSMA prior to RP is safe and effective, concluded Dr. Bolton. The radiation dose delivered to the primary tumour and surrounding lymph nodes is high, although somewhat variable. Responses are encouraging from a biochemical, imaging, and pathological perspective. Based on these findings, further research in this area is justified. While not a panacea, he said, LuPSMA could become an important component of personalized therapy and appears to have very few limitations. Further trials are forthcoming, and this modality offers an opportunity for urologists to take a leading role in PCa care.

During a Q&A, an attendee asked whether LuPSMA should be used before or after surgery, given the late effect of lutetium-177 on tissue. Dr. Bolton replied that all the lutetium-177 should be out of the system by 6 weeks, but if it were taken up by bone marrow or other tissues, then fitness for surgery might be affected. The full 3-year results of LuTectomy will provide further insight but, to date, there is no indication that there are downsides to using LuPSMA in the neoadjuvant setting.

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Abbreviations

ADT	androgen deprivation therapy
BCR	biochemical recurrence
CI	confidence interval
CT	computed tomography
DRE	digital rectal examination
EAU	European Association of Urology
ePLND	extended pelvic lymph node dissection
HR	high risk

IR	intermediate risk
LND	lymph node dissection
LR	low risk
LuPSMA	lutetium-177 PSMA-617 radionucleotide
LUTS	lower urinary tract symptoms
MFS	metastasis-free survival
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
OR	odds ratio
OS	overall survival
PCa	prostate cancer
PET	positron emission tomography
PI-RADS	Prostate Imaging-Reporting and Data System
PLND	pelvic lymph node dissection
PPUI	post-prostatectomy urinary incontinence
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RCT	randomized controlled trial
RP	radical prostatectomy
RT	radiotherapy
SUVmax	maximum standardized uptake value
TRUS	transrectal ultrasound

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